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## **Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion**

Dummer, R ; Ascierto, P A ; Basset-Seguin, N ; Dréno, B ; Garbe, C ; Gutzmer, R ; Hauschild, A ; Krattinger, R ; Lear, J T ; Malvey, J ; Schadendorf, D ; Grob, R J J

**Abstract:** Sonidegib and vismodegib are hedgehog pathway inhibitors (HhIs) approved for the treatment of advanced basal cell carcinoma (BCC). Until recently, vismodegib was the only targeted treatment available for patients with locally advanced BCC (laBCC) in cases where surgery and radiotherapy are inappropriate. Sonidegib has recently been approved and now presents an alternative treatment option. The clinical differences between the two HhIs in patients with laBCC are unclear, as no head-to-head randomized controlled trials are or will be initiated. Moreover, there were important differences in the designs of their pivotal studies, BOLT (sonidegib) and ERIVANCE (vismodegib), and these differences complicate evidence-based analysis of their relative efficacy and safety profiles. In this paper, a group of clinical experts in the management of laBCC summarizes the clinical and pharmacological profiles of sonidegib and vismodegib based on published data and their own clinical experience. One key difference between the two pivotal studies was the criteria used to assess BCC severity. ERIVANCE (a single-arm phase II trial) used the conventional Response Evaluation Criteria in Solid Tumors (RECIST), while the more recent double-blind randomized BOLT trial used the stringent modified RECIST (mRECIST). A pre-planned analysis adjusted the outcomes from BOLT with RECIST-like criteria and this enabled the experts to discuss relative efficacy outcomes for the two treatments. Centrally reviewed objective response rate (ORR) for vismodegib was 47.6% (95% CI 35.5-60.6) at 21-month follow-up using RECIST. After adjusting with RECIST-like criteria, the ORR for sonidegib according to central review at 18-month follow-up was 60.6% (95% CI 47.8-72.4). Both treatments were associated with similar patterns of adverse events. Sonidegib and vismodegib share the same efficacy and tolerability profiles, but their pharmacokinetic profiles show several differences, such as volume of distribution and half-life. Further studies are needed to understand how these differences may impact clinical practice.

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# **Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion**

**Running head:** A joint expert opinion on sonidegib and vismodegib

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## **Conflict of Interest**

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<b>Text</b>	3,047 words (excl. acknowledgement)	3000 words
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## Abstract

Sonidegib and vismodegib are hedgehog pathway inhibitors (HhIs) approved for the treatment of advanced basal cell carcinoma (BCC). Until recently, vismodegib was the only targeted treatment available for patients with locally advanced BCC (laBCC) in cases where surgery and radiotherapy are inappropriate. Sonidegib has recently been approved and now presents an alternative treatment option. The clinical differences between the two HhIs in patients with laBCC are unclear, as no head-to-head randomized controlled trials are or will be initiated. Moreover, there were important differences in the designs of their pivotal studies, BOLT (sonidegib) and ERIVANCE (vismodegib), and these differences complicate evidence-based analysis of their relative efficacy and safety profiles. In this paper, a group of clinical experts in the management of laBCC summarizes the clinical and pharmacological profiles of sonidegib and vismodegib based on published data and their own clinical experience. One key difference between the two pivotal studies was the criteria used to assess BCC severity. ERIVANCE (a single-arm phase II trial) used the conventional Response Evaluation Criteria in Solid Tumors (RECIST), while the more recent double-blind randomized BOLT trial used the stringent modified RECIST (mRECIST). A pre-planned analysis adjusted the outcomes from BOLT with RECIST-like criteria and this enabled the experts to discuss relative efficacy outcomes for the two treatments. Centrally reviewed objective response rate (ORR) for vismodegib was 47.6% (95% CI 35.5–60.6) at 21-month follow-up using RECIST. After adjusting with RECIST-like criteria, the ORR for sonidegib according to central review at 18-month follow-up was 60.6% (95% CI 47.8–72.4). Both treatments were associated with similar patterns of adverse events. Sonidegib and vismodegib share the same efficacy and tolerability profiles, but their pharmacokinetic profiles show several differences, such as volume of distribution and half-life. Further studies are needed to understand how these differences may impact clinical practice.

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## Introduction

Basal cell carcinoma (BCC) is the most common form of cancer in the Caucasian population.<sup>1</sup> Most BCCs can be removed by surgery, but occasionally they progress deep into the tissue or metastasize to the extent where curative surgery and radiotherapy are not feasible.<sup>1-4</sup> In a systematic analysis at one tertiary referral center, locally advanced BCC (laBCC) comprised <1% of all BCCs in almost 10,000 patients<sup>4</sup>. In some patients with laBCC, surgical intervention can result in disfiguring deformity, loss of function and morbidity<sup>3-7</sup>, and Nägeli and Dummer have proposed criteria to help define when surgery and irradiation is inappropriate (Table 1).<sup>8</sup>

Multidisciplinary care is essential in the management of laBCC, and effective communication is vital to ensure patients have realistic expectations from their treatment. Alongside effective adverse effect (AE) management, pre-treatment education about potential AEs increases the likelihood that patients will tolerate optimal treatment durations.

Aberrant signaling of the hedgehog pathway is important to the pathophysiology of BCC<sup>1,7</sup> and two licensed hedgehog pathway inhibitors (HhIs), sonidegib and vismodegib, are indicated for the treatment of laBCC in cases where surgery and radiotherapy are inappropriate.

Vismodegib was EMA-approved for treatment of laBCC and symptomatic metastatic BCC based on outcomes from the ERIVANCE study.<sup>9,10</sup> Sonidegib, which is comparatively new to the market, gained EMA-approval for laBCC treatment based on the results of the BOLT study.<sup>11,12</sup> Although these two agents act on the same pathway and have similar indications, there are currently no evidence-based recommendations to help clinicians choose between them, as there are no randomized, controlled trials comparing sonidegib with vismodegib and the pivotal phase II studies, BOLT and ERIVANCE, did not compare the HhIs with standard of care.<sup>9,11</sup> Thus, the clinical differences between sonidegib and vismodegib in patients with laBCC remain unclear. A 2017 analysis attempted to provide an indirect

comparison between sonidegib and vismodegib by using statistical methods to reduce potential confounders between the two pivotal studies.<sup>13</sup> However, while this study adjusted for some key differences in patient baseline characteristics, it did not consider numerous other important differences between BOLT and ERIVANCE.<sup>13</sup>

Without head-to-head comparisons, an expert discussion using the published data on sonidegib and vismodegib is valuable in understanding their relative study outcomes, without introducing additional statistical analyses or further confounders. The expert panel of this review paper is made up of clinicians who are internationally recognized experts in the treatment of laBCC, and are involved in developing national and/or international non-melanoma guidelines, together with a pharmacologist. All the experts are from countries where both HhIs have been approved for the treatment of laBCC.

### **Sonidegib and vismodegib have different pharmacokinetic profiles**

Studies into the pharmacokinetic profiles of sonidegib and vismodegib have shown several differences. Sonidegib and vismodegib demonstrate a high level of binding (>99%) to the plasma proteins alpha-1-acid glycoprotein (AAG) and human serum albumin (HSA).<sup>10,12,14</sup> However, the plasma protein binding of sonidegib within a dose range of 200–800 mg was non-concentration-dependent, whereas vismodegib at 150 mg or higher demonstrated concentration-dependent binding.<sup>15–17</sup> Overall, vismodegib plasma levels strongly correlated with AAG plasma levels, due to saturable, highly reversible drug-protein binding. Once saturated, vismodegib showed further low-affinity binding to the high-capacity binder HSA.<sup>15,16,18</sup> Therefore, vismodegib 150 mg delivered the maximum serum concentration and a higher dosage will not increase the unbound drug level in the plasma (Fig. 1).<sup>17</sup> In contrast, increasing sonidegib dosage resulted in increasing level of unbound, active drug in the plasma until dose-limited absorption occurred.<sup>19</sup>

Vismodegib has a volume of distribution of 16–27 liters, suggesting that it is largely confined to the plasma and has limited tissue penetration.<sup>10,20</sup> In contrast, sonidegib seems to be more lipophilic than vismodegib and has a volume of distribution of >9,000 liters, indicating extensive distribution in the tissues.<sup>12,19,21</sup> Consequently, the concentration of sonidegib is six-times higher in skin than in plasma.<sup>12</sup> In theory, these evidences suggest that sonidegib is more extensively distributed in the skin compared with vismodegib, which may explain potential differences in efficacy and toxicity between them.

Sonidegib has a long elimination half-life of 28–30 days and achieves steady state after 3–4 months.<sup>12,19,22</sup> In contrast, vismodegib has a half-life of 4–12 days and achieves steady state after 7–21

days.<sup>10,18–20,22</sup> In general, the more extended the half-life, the longer it takes to reach steady state and maximum effect, and AEs will take longer to subside on stopping treatment.

However, further studies are needed to compare the impact of dosage titration (both up and down-titration) between sonidegib and vismodegib.

### **BOLT and ERIVANCE are appropriate for comparative discussion**

The BOLT study was a multicenter, international, randomized, double-blind, pivotal, phase IIb clinical trial assessing the efficacy and safety of sonidegib, with a primary endpoint of overall response rate (ORR) determined by MRI and multiple biopsies via central review.<sup>11</sup> Although BOLT participants were randomized 1:2 to sonidegib 200 mg or 800 mg, the expert panel discussion focused on outcomes of sonidegib 200 mg in patients with laBCC because this is the approved dose and indication.<sup>11,12</sup>

ERIVANCE was a non-randomized, single-arm multicenter, international, pivotal, phase IIb clinical trial assessing the efficacy and safety of vismodegib 150 mg in patients with laBCC and metastatic BCC, with ORR by central review as the primary endpoint.<sup>9</sup>

Vismodegib was also assessed in two other phase II studies, STEVIE AND MIKIE.<sup>23,24</sup> However, because of important differences (summarized in Table 2), the expert group considered that data from these studies were not appropriate for head-to-head comparison of efficacy and their review therefore focused on the pivotal studies, ERIVANCE and BOLT.

ERIVANCE and BOLT had similar baseline patient characteristics, and both used ORR by central review as the primary endpoint (Table S1, supporting information).<sup>9,11</sup> However, beyond this, there are many important differences between these studies (Table 2).<sup>9,11</sup>

### **BOLT endpoints assessment criteria were more stringent compared with ERIVANCE**

#### **i. Complete, partial and overall response rates**

There are important differences between BOLT and ERIVANCE regarding lesion assessment and this has complicated evidence-based analysis of the relative efficacy and safety of sonidegib and vismodegib. Since some BCCs demonstrate slow growth, it can be difficult to differentiate stable disease (SD) from progressive disease (PD), particularly over short assessment periods. In addition, regressed lesions present scar-like plaques, which can be difficult to differentiate complete response (CR) from partial response (PR). In order to reduce the risk of this bias, this review focuses on ORR, defined as the proportion of patients with a best overall response of CR or PR.

## ii. Investigator review vs central review

BOLT and ERIVANCE both assessed response by central and investigator review (Fig. 2).<sup>9,11</sup> In general, investigator review showed more positive outcomes than central review.<sup>9,11,15,25,26</sup> In the primary analysis of ERIVANCE, the concordance between assessment by central review and investigator review was 60%; ORR by central review was 42.9% (95% CI 30.5–56.0), with 20.6% CR and 22.2% PR, whereas ORR by investigator review was 60.3% (95% CI 47.2–71.7), with 31.7% CR and 28.6% PR.<sup>9</sup> Similar trends were observed in BOLT and in subsequent follow-ups in both studies (Table S2, S3, supporting Information).<sup>9,11,15,25,26</sup> Central review is more rigorous and was the primary endpoint of both pivotal studies, and is thus more appropriate for comparison.

## iii. RECIST vs mRECIST

ERIVANCE used the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 protocol, while BOLT used modified RECIST (mRECIST) criteria (Table 3).<sup>9,11,27,28</sup> There is no evidence to support mRECIST being more reproducible than RECIST, but mRECIST is considered to have more stringent evaluation criteria and is more likely to detect minimal signs of disease and disease progression (Table 4).<sup>25</sup> Therefore, mRECIST may classify a given treatment response as partial, whereas the same response may be considered as complete using RECIST. Similarly, mRECIST is more likely to detect signs of slight disease progression that may be classified as SD under RECIST. The use of these different evaluation criteria adds a further complication to comparing outcomes between the trials. However, BOLT included a pre-planned analysis which adjusted study outcomes with RECIST-like criteria, similar to those used in ERIVANCE.<sup>15</sup>

## iv. Follow-up period

The follow-up periods were different between the two studies and there were no reported outcomes with the same minimum follow-up period (Fig. 2).<sup>9,11,15,25,26,29</sup> The closest follow-up time points across the studies were the 18-month analysis for BOLT and the 12-month update (21-month follow-up) for ERIVANCE.<sup>9,11,15,25,26,29</sup>

As a result of all these inter-study variations, the expert panel considered the most representative data for discussion were the ORRs based on RECIST criteria by central review at 18–21-month follow-up. The outcomes from the final analyses were not considered appropriate for discussion, as ERIVANCE did not include a central review at the 30-month update.

## **Sonidegib and vismodegib share a similar efficacy profile**



In BOLT, 66 patients with laBCC were treated with sonidegib 200 mg, and in ERIVANCE, 63 patients with laBCC were treated with vismodegib 150 mg.<sup>9,11</sup> The baseline demographics and patient characteristics between the two studies were similar, with key differences being the greater number of patients with prior surgery and prior radiotherapy in ERIVANCE (Table S1, supporting information).<sup>9,11</sup>

At the initial 9-month follow-up of ERIVANCE, the primary endpoint (ORR by central review using RECIST) for vismodegib 150 mg was 42.9% (95% CI 30.5–56.0), with 20.6% CR and 22.2% PR (Table S3, supporting information).<sup>9</sup> At the 21-month follow-up, ORR increased to 47.6% (95% CI 35.5–60.6), with 22.2% CR and 25.4% PR (Table 5).<sup>26</sup> The final outcomes of ERIVANCE at 39-months were reported by investigator review only.<sup>29</sup>

Based on the US Food and Drug Agency recommendation, the BOLT study of sonidegib used mRECIST criteria determined by central review and reported an ORR of 47.0% (95% CI 34.6–59.7) at primary 6-month follow-up, with 3.0% CR and 43.9% PR, increasing to 56.1% (95% CI 43.3–68.3) at 18-month follow-up, with 4.5% CR and 51.5% PR (Table S2, supporting information).<sup>11,15</sup> At long-term follow up (30 months) sonidegib was associated with an ORR of 56.1% (95% CI 43.3–68.3); 4.5% CR and 51.5% PR.<sup>15</sup>

After adjusting the response in BOLT using RECIST-like criteria, ORR by central review for sonidegib at 18 months increased by a small proportion from 56.1% (CR, 4.5%; PR, 51.5%) to 60.6% (CR, 22.7%; PR, 37.9%) (Table 6).<sup>15</sup> In contrast, CR increased 5-fold using the less stringent RECIST-like criteria.<sup>15</sup> Similar trends were observed in the primary analysis and 30-month follow-up (Table S3, S4, supporting information). This increase in CR was primarily due to lesions previously considered as PR under mRECIST being considered CR under RECIST-like criteria (Fig. 3). The adjusted CR rate was similar to that observed in ERIVANCE at 21-months.<sup>15,26</sup>

The centrally reviewed median duration of response (mDOR) and median progression-free survival (mPFS) with sonidegib in BOLT were higher than those observed with vismodegib in ERIVANCE.<sup>15,26</sup> Ideally, data from the final analyses of the two pivotal studies should be used to review mDOR and mPFS. However, the study outcomes for vismodegib at the final analysis were only reported by investigator review, so 21-month follow-up data were used for discussion instead. The centrally reviewed mDOR was 26.1 months (95% CI NE) with sonidegib at 30-month follow-up and 9.5 months (95% CI 7.4–21.4) with vismodegib at 21-month follow-up (Table 7, Fig. 4).<sup>10,15,26</sup> In the investigator review, the mDOR was 15.7 months (95% CI 12.9–20.2) with sonidegib at 30-month follow-up and 26.2 months (95% CI 9.0–37.6) with vismodegib at 39-month follow-up (Table S2,S3, supporting information).<sup>10,15,29</sup> The centrally reviewed mPFS was 22.1 months (95% CI NE) with sonidegib at 30-

month follow-up and 9.5 months (95% CI 7.4–14.8) with vismodegib at 21-month follow-up (Table 7, Fig. 5).<sup>15,26</sup> In the investigator review, the mPFS was 19.4 months (95% CI 16.6–23.6) with sonidegib at 30-month follow-up and 12.9 months (95% CI 10.2–28.0) with vismodegib at 39-month follow-up (Table S2,S3, supporting information).<sup>15,29</sup> The estimated overall survival (OS) was 93.2% at 30-month follow-up with sonidegib (Table S2, supporting information) and the estimated OS was 85.5% at 39-month follow-up with vismodegib (Table S3, supporting information).<sup>15,29</sup>

These outcomes in laBCC patients were based on different lengths of treatment exposure, as well as two separate studies, which added complexity to drawing a conclusion. Analyses of quality of life (QoL) results are not reported here but they are included in the discussion.

### **Sonidegib and vismodegib share a similar tolerability profile**

At the final 39-month data cut-off in ERIVANCE, patients' median duration of exposure to vismodegib was 12.9 months and 96 of 104 patients with laBCC or mBCC treated with vismodegib 150 mg discontinued their treatment.<sup>29</sup> About 57% of patients had discontinued vismodegib 150 mg due to AEs or physicians'/patients' decision by 39 months.<sup>29</sup> All patients experienced  $\geq 1$  treatment emergent AEs (TEAEs).<sup>29</sup> Similar rates of discontinuation were observed in BOLT, where patients' median duration of exposure to sonidegib was 11.0 months at the final 30-month analysis and 73 of 79 patients with laBCC or mBCC treated with sonidegib 200 mg discontinued their treatment.<sup>15</sup> About 53% of patients had discontinued sonidegib 200 mg due to AEs or physicians'/patients' decision by 30 months.<sup>15</sup> In both studies, AEs were the primary reason for patients' and physicians' decisions to discontinue treatment.<sup>15,29</sup>

Over half of the patients with laBCC or mBCC treated with vismodegib 150 mg in ERIVANCE at 39-months experienced AEs including muscle spasms (71.2%), alopecia (66.3%), dysgeusia (55.8%) and weight loss (50.0%) (Table S5, supporting information).<sup>29</sup> Most AEs were mild. The most frequent grade  $\geq 3$  AE was weight loss (8.7%), follow by muscle spasms (5.8%) and fatigue (4.8%) (Table S5, supporting information).<sup>29</sup> The shortest median time to onset of AEs with vismodegib 150 mg was dysgeusia at 1.48 months (95% CI 0.99–2.07), followed by muscle spasm at 1.89 months (95% CI 1.35–2.73) (Fig. 6).<sup>26</sup> Median time to onset of weight loss was the longest, at 6.13 months (95% CI 4.5–7.36).<sup>26</sup>

At 30-months, the most commonly reported TEAEs (any grade) in patients with laBCC or mBCC treated with sonidegib 200 mg (n=79) were muscle spasms (54.4%), alopecia (49.4%) and dysgeusia (44.3%) (Table S5, supporting information).<sup>15</sup> Most AEs were mild. The most frequent grade  $\geq 3$  AEs were

elevated CK (6.3%), weight loss (5.1%) and muscle spasms (2.5%) (Table S5, supporting information).<sup>15</sup> The shortest median time to onset of AEs with sonidegib 200 mg was fatigue at 1.08 months (95% CI 0.53–3.6), followed by muscle spasm at 2.07 months (95% CI 1.87–3.19) (Fig. 6).<sup>30</sup> The longest median times to onset of AEs were diarrhea (95% CI 1.35–10.32) and weight loss (95% CI 4.70–8.31) at 6.47 months.<sup>30</sup>

Initial assessment of published data from both pivotal studies showed that sonidegib had an approximately 10% lower incidences of most AEs compared with vismodegib at final analyses.<sup>15,29</sup> Overall, TEAEs reported with sonidegib were slightly less frequent and less severe compared with vismodegib.<sup>15,29</sup> The time to onset of AEs also indicated that patients treated with sonidegib may experience AEs slightly later than with vismodegib, with the exception of fatigue (Fig 6).<sup>15,26,29,30</sup> However, as these data cannot be directly compared, the above can only serve as indicative values. In general, sonidegib and vismodegib are associated with similar patterns of AEs, suggesting HhI class-dependent effects.<sup>15,26,29,30</sup>

#### **Further studies are needed to provide a conclusive outcome**

The key clinical questions regarding sonidegib and vismodegib focus around their relative risk–benefits and whether switching between the two HhIs could be useful.

One of the most important differences between these agents is their pharmacokinetic profile. Sonidegib at 200 mg and 800 mg demonstrated non-concentration-dependent plasma protein binding, whereas vismodegib at 150 mg or higher demonstrated concentration-dependent plasma protein binding.<sup>15–17</sup> Sonidegib has a longer half-life (28–30 days) and higher volume of distribution (>9000 liters) than vismodegib (4–12 days and 16–27 liters, respectively).<sup>10,12,19–21</sup> How these differences may impact the use of these HhIs in clinical practice remains an open question. For example, the differences in time to steady state and plasma concentration between the two HhIs do not seem to correlate with the effect of the drugs – the median time to response was 3.9 months for sonidegib in BOLT and 5.6 months for vismodegib in ERIVANCE.<sup>9,11</sup> However, sonidegib demonstrated a longer time to AE onset (except for fatigue), with even less frequent and less severe AEs compared with vismodegib.<sup>26,29,30</sup> Nevertheless, it was suggested that switching between the two HhIs is unlikely to be useful from a safety perspective, as the two drugs showed the same mode of action and similar patterns of AEs.

Key methodological differences between BOLT and ERIVANCE meant that only specific datasets were selected for discussion, and data from the pre-planned analysis from BOLT was used to aid comparison. The mRECIST criteria used in BOLT was considered more stringent compared with

RECIST.<sup>25</sup> Nevertheless, the centrally reviewed ORR in BOLT at 18-months was comparable using either set of lesion assessment criteria, while the rate of CR increased with RECIST-like criteria.<sup>15</sup> This adjusted CR rate was similar to those observed in ERIVANCE at 21-months.<sup>15,26</sup> The centrally reviewed mDOR and mPFS with sonidegib at 30-months were longer than vismodegib at 21-months.<sup>15,26</sup> In the investigator review, vismodegib demonstrated a longer mDOR, but shorter mPFS at 39-months compared with sonidegib at 30-months.<sup>10,15,26</sup> However, these data are only indicative of the comparative efficacy profiles of the two HhIs, as they were based on different treatment exposure lengths from two separate studies.

Patients with laBCC treated with sonidegib demonstrated sustained or improved QoL in BOLT, despite development of AEs.<sup>11,25,31</sup> Patients with laBCC treated with vismodegib showed no positive changes from baseline on either the physical or emotional portions of the Short Form-36 questionnaire in ERIVANCE.<sup>31,32</sup> However, these data cannot be compared, as different health-related QoL scales were used and the assessment frequency also differed. A review of the QoL outcomes from the STEVIE study showed that vismodegib was associated with clinically meaningful improvement in the emotional domain using the Skindex-16 scale.<sup>33</sup> However, differences in isolated health-related QoL scale dimensions may result in bias and should not be compared.

In the absence of a head-to-head comparison study, the clinical relevance of pharmacokinetic profile of sonidegib needs further studies to provide conclusive evidence. Intermittent trials, sequential trials or cross-over trials of the two HhIs, in laBCC patients who discontinued treatment due to AEs, may demonstrate the impact of the pharmacokinetic profiles. Further exploratory studies of real-world populations may shed light on how pharmacokinetic profile differences may affect the use of sonidegib and vismodegib in clinical practice.

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data in the first draft manuscript but had no further involvement in the development of the manuscript. All authors reviewed drafts of the manuscript and further developed the concept. Havas Life Medicom subsequently supported incorporation of comments into the final draft for author approval. All authors read and approved the final version for submission.

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Table 1 Criteria to define when surgery and irradiation is inappropriate in laBCC.<sup>8</sup>

<ul style="list-style-type: none"> <li>• &gt;5 BCCs, if patient suffers from genetic syndromes</li> </ul>
<ul style="list-style-type: none"> <li>• BCC &gt;10 mm, relapsing after 2 surgeries in critical locations (e.g. periocular and perioral areas)</li> </ul>
<ul style="list-style-type: none"> <li>• BCC infiltrating in bone/cartilage/other structures and curative resection unlikely</li> </ul>
<ul style="list-style-type: none"> <li>• Relapsing BCC after multiple surgeries and/or radiotherapy</li> </ul>
<ul style="list-style-type: none"> <li>• Advanced BCC in patients who do not qualify for general anesthesia</li> </ul>

BCC, basal cell carcinoma; laBCC, locally advanced BCC.

Table 2 Overview of sonidegib and vismodegib clinical trials in patients with locally advanced basal cell carcinoma.

	BOLT <sup>11</sup>	ERIVANCE <sup>9</sup>	STEVIE <sup>23</sup>	MIKIE <sup>24</sup>
Treatment	Randomized 1:2 to sonidegib 200 mg QD (laBCC, n=66) or 800 mg QD (laBCC, n=128)	Vismodegib 150 mg QD (laBCC, n=63)	Vismodegib 150 mg QD (laBCC, n=1,119)	Randomized 1:1 to vismodegib 150 mg QD in an intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo (n=116) or 24 weeks induction followed by an intermittent schedule of 8 weeks placebo followed by 8 weeks vismodegib (n=113)
Inclusion criteria	<p>≥18 years old</p> <p>Inoperable laBCC or surgery is contraindicated and radiotherapy is contraindicated or inappropriate</p> <p>Adequate bone marrow, liver, and renal function</p>	<p>≥18 years old</p> <p>Inoperable laBCC and prior radiotherapy, unless radiotherapy is contraindicated or inappropriate</p>	<p>≥18 years old</p> <p>Inoperable laBCC or surgery is contraindicated and radiotherapy is contraindicated or inappropriate</p> <p>ECOG Performance Status 0–2</p>	<p>≥18 years old</p> <p>Multiple BCC, including participants with Gorlin syndrome, with at least 6 clinically evident BCC lesions (3 of which measured ≥5mm in diameter)</p> <p>ECOG Performance Status 0–2</p> <p>Adequate renal and hepatic function and hematopoietic capacity</p>
Exclusion criteria	Major surgery within 4 weeks of	Major organ dysfunction	Concurrent anti-tumor therapy	Inoperable laBCC or surgery is

initiation of study medication	Pregnancy or lactation	Completion of the most recent anti-tumor therapy less than 21 days prior to the initiation of treatment	contraindicated and radiotherapy is contraindicated or inappropriate
Pregnancy or lactation	Participation in an investigational study in the previous 4 weeks	Uncontrolled medical illness	mBCC
Participation in an investigational study in the previous 4 weeks	Life expectancy of <12 weeks		Pregnancy or lactation
Concurrent therapy with other anti-neoplastic agents	Superficial multifocal BCC, which may be considered unresectable due to breadth of involvement		Participation in an investigational study in the previous 4 weeks
Neuromuscular disorders or concurrent drugs that may cause muscle damage	Uncontrolled medical illnesses that would contraindicate the use of the investigational drug and an inability to swallow capsules		Known or suspected alcohol abuse
Concurrent medical conditions that may interfere or potentially affect the interpretation of the study			One of the following known rare hereditary conditions: galactose intolerance, primary hypolactasia or glucose-galactose malabsorption
Oral drugs or lack of physical integrity of the upper gastrointestinal tract, or known malabsorption syndromes	Concurrent antitumor therapy		

BCC assessment criteria	mRECIST	RECIST	RECIST	–
Primary endpoint	ORR (CR+PR) by central review	ORR (CR+PR) by central review	Safety	Mean percent change from baseline in the number of clinically evident BCC
Secondary endpoints	ORR by investigator review  DOR  PFS  OS  Time to response  Safety  QoL	ORR by investigator review  DOR  PFS  OS  Safety  QoL	ORR by investigator review  DOR  PFS  OS  Time to response  QoL	Safety  QoL  Mean percent change from baseline in total size of three target BCC lesions  Percentage of patients with at least 50% reduction in the number of BCC  Percentage of patients with new BCC lesions  Percent change in total number of BCC relative to baseline at Week 85, 97 and 125

CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; laBCC, locally advanced basal cell carcinoma; mRECIST; modified RECIST; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; QD, once daily; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3 Evaluation of Target Lesions by RECIST V1.0 and mRECIST.

	mRECIST* <sup>28</sup>	RECIST V1.0 <sup>27</sup>
CR	Histology: negative $\geq 2$ biopsies (fresh tumor biopsy specimens were required to confirm a complete response) Photograph/MRI: complete disappearance of target lesion	Histology: negative $\geq 1$ biopsies Photograph/MRI (unidimensional): partial response or stable disease allowed
PR	Photograph (bidimensional): $\geq 50\%$ reduction in the sum of products of perpendicular diameters per WHO MRI (unidimensional): $\geq 30\%$ reduction in the sum of diameters of all target lesions per RECIST v1.1	Photograph/MRI (unidimensional): $\geq 30\%$ reduction in the longest diameter of externally visible or radiographic dimension (if applicable, per RECIST v1.0) or complete resolution of ulceration
PD	Photograph/MRI (unidimensional): $\geq 25\%$ increase in the sum of the longest diameter	Photograph/MRI (unidimensional): $\geq 20\%$ increase in the sum of the longest diameter
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD

BCC, basal cell carcinoma; CR, complete response; laBCC, locally advanced basal cell carcinoma; mRECIST, modified RECIST; MRI, magnetic resonance imaging; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease, WHO; World Health Organization.

\*mRECIST is a composite multimodal evaluation used to integrate MRI according to RECIST V1.1, standard and annotated color photography using WHO criteria, and histology in multiple biopsies based on lesion surface area in the complex setting of posttreatment scarring, fibrosis, and ill-defined lesion borders.

Table 4 Composite overall response in laBCC determined by mRECIST and RECIST-like criteria.

MRI*	Photograph†	Histology‡	Composite overall response	
			mRECIST§	BCC-RECIST-like
CR	CR	Negative	CR	CR
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative		
	Not available	Negative		
NA	CR	Negative	CR	CR
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative		
PR	CR	Negative	PR	CR
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative		
	Not available	Negative		
SD	CR	Negative	PR	CR
	PR (scar/fibrosis only) or SD (scar/fibrosis only)	Negative		
CR	PR	Negative	PR	CR
PR				
SD				
NA				
CR	SD	Negative	SD	CR
PR				
CR	CR	Positive or unknown	PR	PR
	PR			
	PR (scar/fibrosis only)			
	NA			
PR	CR	Positive or unknown	PR	PR
	PR			
	PR (scar/fibrosis only)			
	NA			
SD	CR	Positive or	PR	PR

	PR	unknown		
	PR (scar/fibrosis only)			
NA	CR	Positive or unknown	PR	PR
	PR			
	PR (scar/fibrosis only)			
CR	SD	Positive or unknown	SD	PR
	SD (scar/fibrosis only)			
PR	SD	Positive or unknown	SD	PR
	SD (scar/fibrosis only)			
SD	SD	Any	SD	SD
	SD (scar/fibrosis only)	Positive or unknown		
	NA	Any		
NA	SD	Any	SD	SD
	SD (scar/fibrosis only)	Positive or unknown		
Any (except PD)	Unknown	Any	Unknown	Unknown
Unknown	Any (except PD)	Any	Unknown	Unknown
PD	Any	Any	PD	PD
Any	PD	Any	PD	PD

BCC, basal cell carcinoma; CR, complete response; laBCC, locally advanced basal cell carcinoma; mRECIST, modified RECIST; MRI, magnetic resonance imaging; NA, not available; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Adapted from "Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study" by JT Lear, *et al.* [CC BY-NC 4.0].

\*Per RECIST v1.1.

†Per World Health Organization criteria.

‡Based on multiple biopsies from lesion surface area.

§An independent review committee re-evaluated all assessments for the laBCC cohort to determine a composite response.

Table 5 Efficacy in patients with laBCC in the BOLT (18-month follow-up) and ERIVANCE (21-month follow-up) studies.

	Sonidegib 200 mg QD <sup>15</sup>	Vismodegib 150 mg QD <sup>26</sup>
	Central review RECIST-like	Central review RECIST
Patients with laBCC	n=66	n=63
ORR n (%); 95% CI	40 (60.6); 47.8–72.4	30 (47.6); 35.5–60.6
CR, n (%)	14 (21.2%)	14 (22.2%)
PR, n (%)	26 (39.4%)	16 (25.4%)
SD, n (%)	20 (30.3%)	22 (34.9%)
PD, n (%)	1 (1.5%)	8 (12.7%)
Unknown, n (%)	5 (7.6%)	3 (4.8%)

BCC, basal cell carcinoma; CR, complete response; laBCC, locally advanced basal cell carcinoma; mRECIST, modified RECIST; ORR, objective response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.



Table 6 Efficacy using mRECIST and RECIST criteria in patients with laBCC treated with sonidegib 200 mg by central review at 18-month follow-up in the BOLT study.

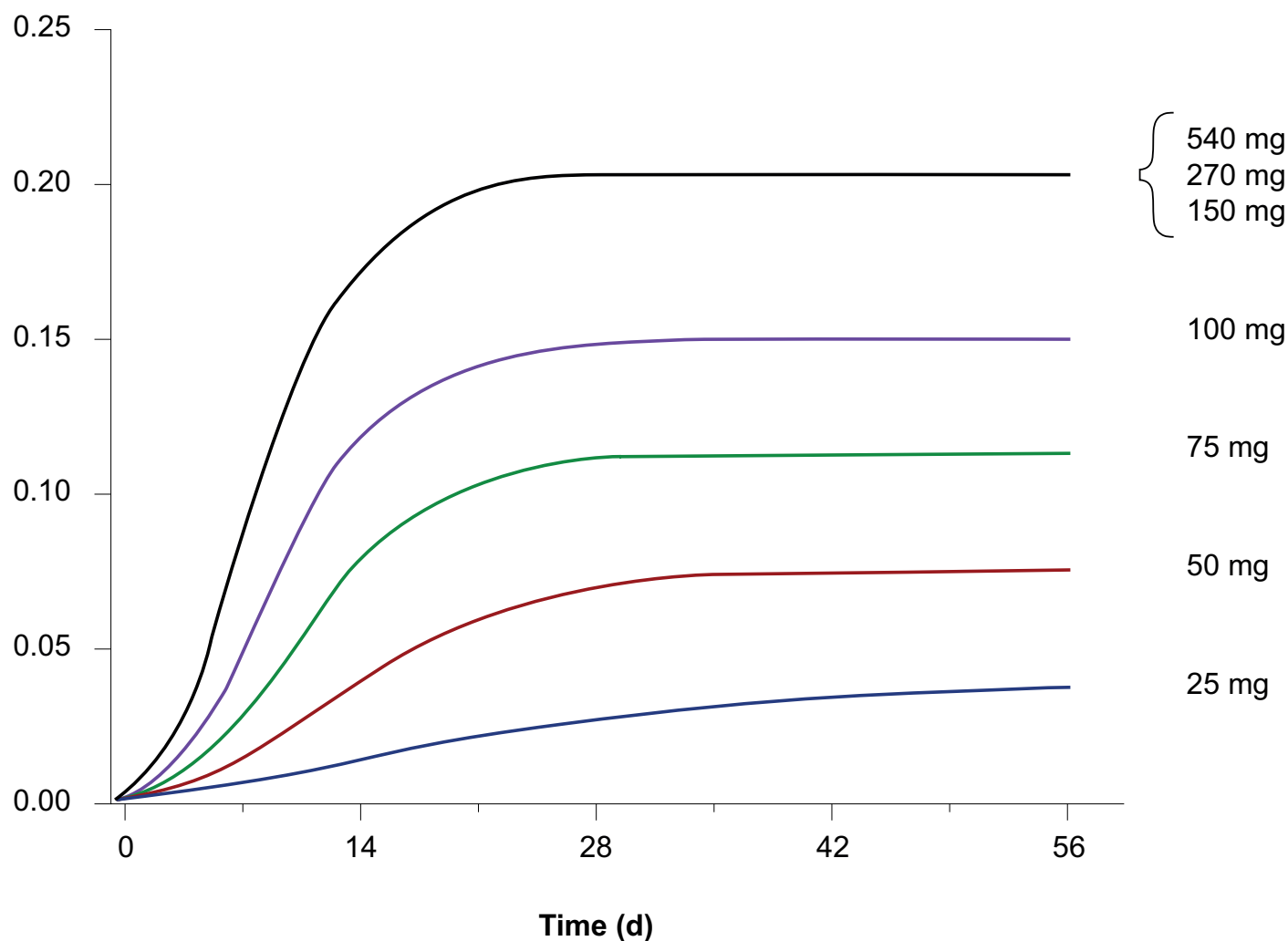
Patients with laBCC	Sonidegib 200 mg QD <sup>15</sup> 18-month follow-up Central review	
	mRECIST n=66	RECIST-like n=66
ORR n (%); 95% CI	(56.1); 43.3–68.3	40 (60.6); 47.8–72.4
CR, n (%)	3 (4.5%)	14 (21.2%)
PR, n (%)	34 (51.5%)	26 (39.4%)
SD, n (%)	23 (34.8%)	20 (30.3%)
PD, n (%)	1 (1.5%)	1 (1.5%)
Unkown, n (%)	5 (7.6%)	5 (7.6%)

CR, complete response; laBCC, locally advanced basal cell carcinoma; mRECIST, modified RECIST; ORR, objective response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Table 7 Duration of response and progression free survival in patients with laBCC treated with sonidegib 200 mg at 30 months and vismodegib 150 mg at 21 months by central review.

	Sonidegib 200 mg QD <sup>15</sup> Central review RECIST-like	Vismodegib 150 mg QD <sup>26</sup> Central review RECIST
Patients with laBCC	n=66	n=63
Follow-up time, Months	30	21
DCR (CR + PR + SD), %	91%	83%
DOR, events/responders	11/37	Not reported
KM median (95% CI), Months	26.1 (NE)	9.5 (7.4–21.4)
PFS, events	16	Not reported
KM median (95% CI), Months	22.1 (NE)	9.5 (7.4–14.8)

CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; KM, Kaplan–Meier; laBCC, locally advanced basal cell carcinoma; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.



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Figure 1. Simulated unbound vismodegib concentration-time profiles after once daily dosing of 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 270 mg, and 540 mg. Doses lower than 150 mg once daily lead to markedly lower unbound vismodegib concentrations. No further increase in vismodegib exposure occurs at doses higher than 150 mg.

d, days.

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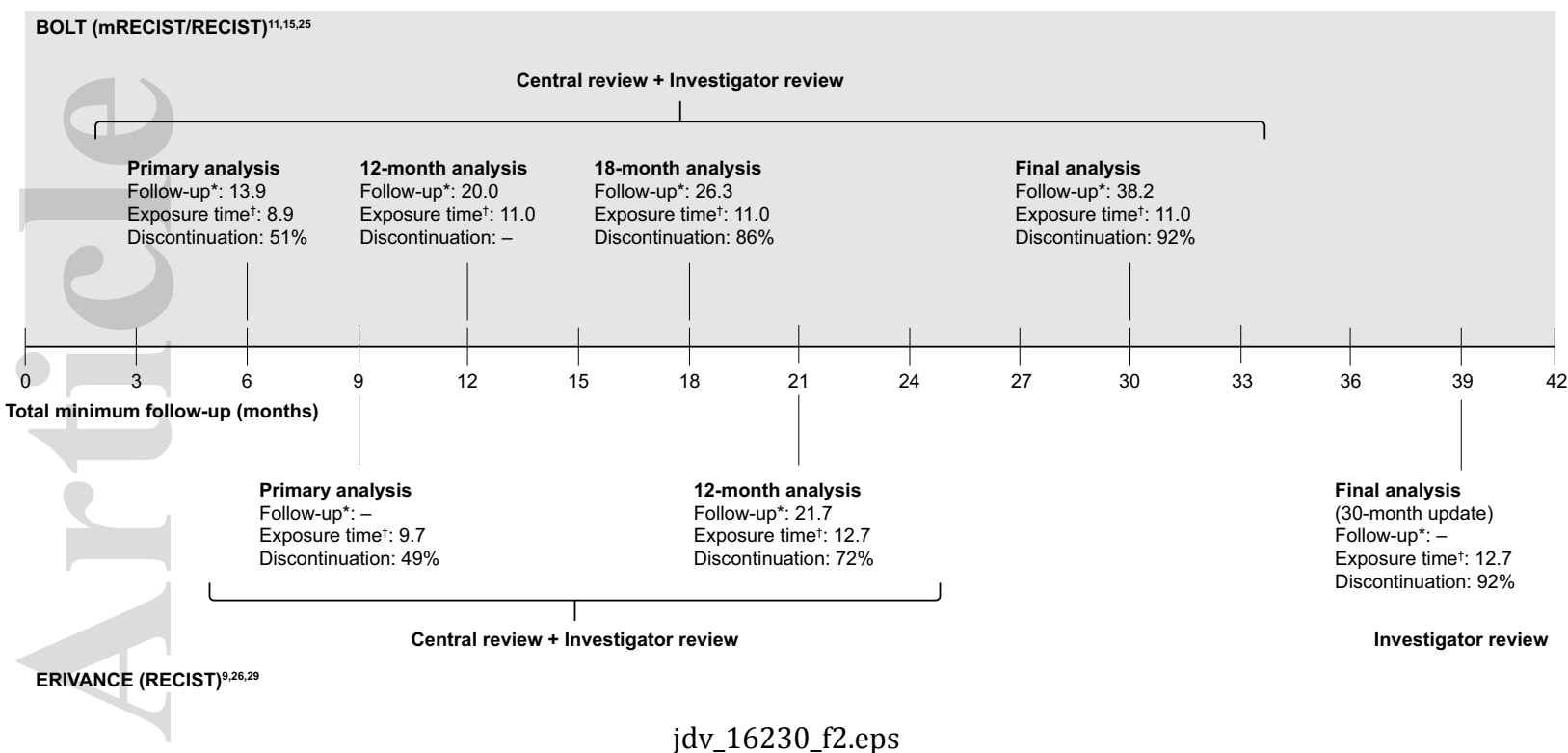


Figure 2. Analyses of the BOLT and ERIVANCE studies in patients with laBCC.

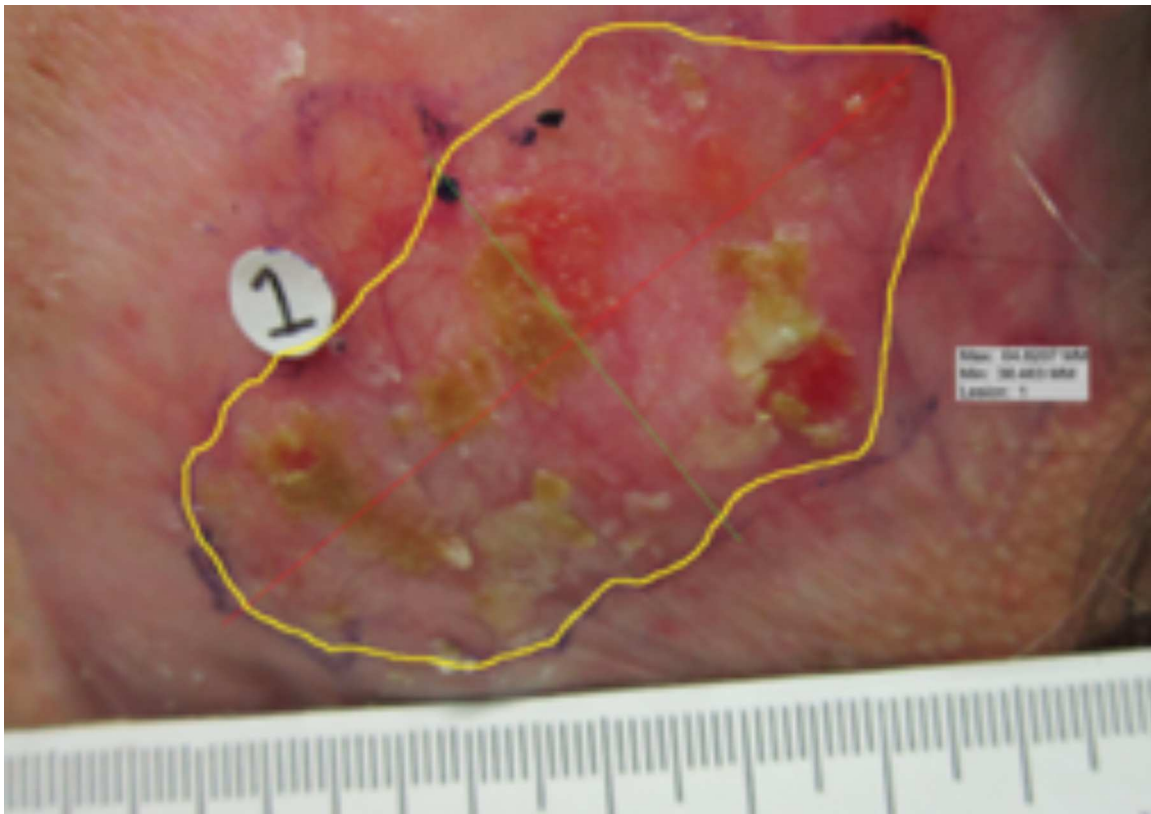
\*Median duration of follow-up (months).  
†Median exposure time (months).



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a)

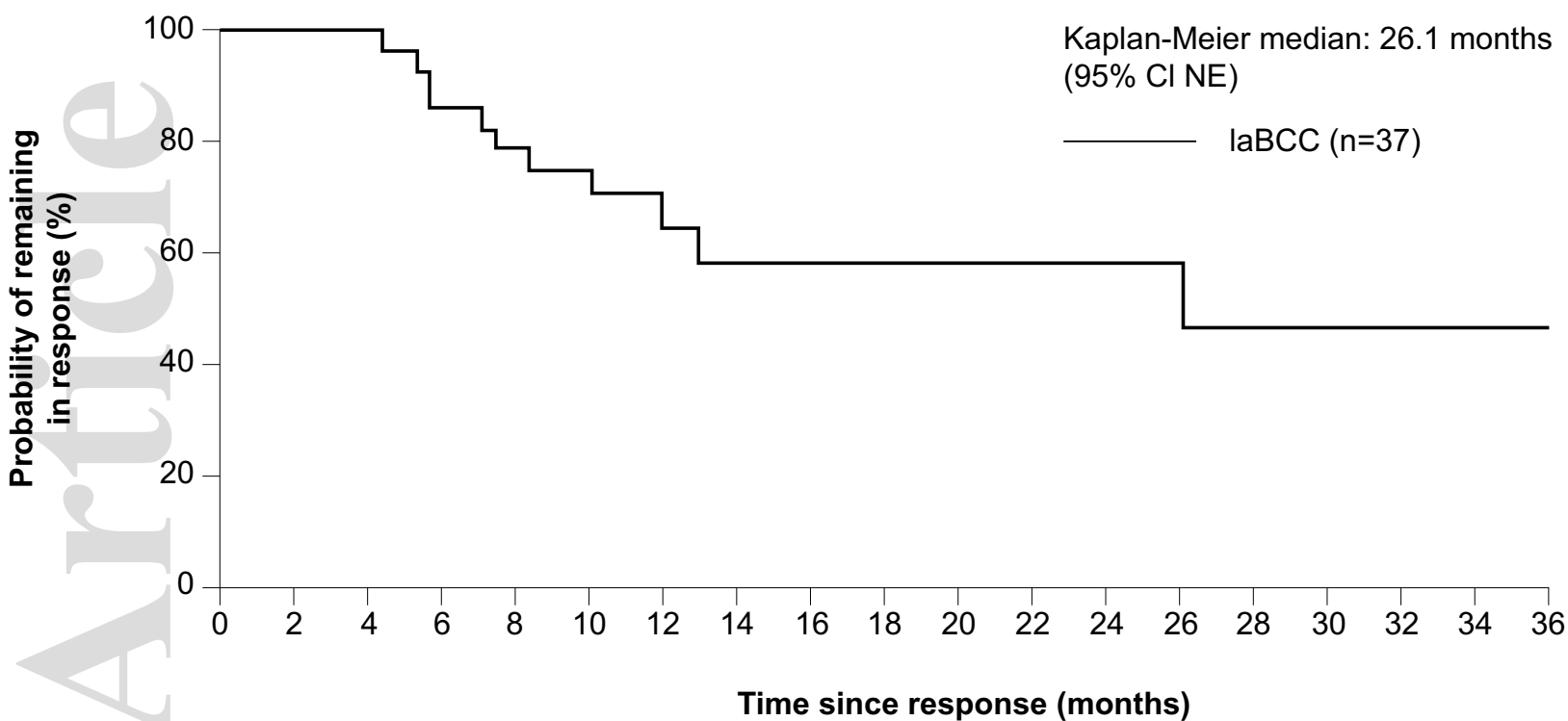
Figure 3. Photographs of locally advanced basal cell carcinoma lesion (LaBCC) and lesion classification using BCC-RECIST-like and mRECIST protocol. a) LaBCC lesion at baseline; b) LaBCC after treatment with sonidegib 200 mg. Lesion response to treatment: MRI and photo assessment showed partial response; negative result on biopsy. Using mRECIST criteria, the composite overall response would be considered a partial response, whereas using BCC-RECIST-like criteria, this is considered a complete response (Table 2). These images are used with the kind permission of Assoc. Prof. A Guminski, Northern Clinical School, Sydney.



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b)

Figure 3. Photographs of locally advanced basal cell carcinoma lesion (LaBCC) and lesion classification using BCC-RECIST-like and mRECIST protocol. a) LaBCC lesion at baseline; b) LaBCC after treatment with sonidegib 200 mg. Lesion response to treatment: MRI and photo assessment showed partial response; negative result on biopsy. Using mRECIST criteria, the composite overall response would be considered a partial response, whereas using BCC-RECIST-like criteria, this is considered a complete response (Table 2).  
These images are used with the kind permission of Assoc. Prof. A Guminski, Northern Clinical School, Sydney.



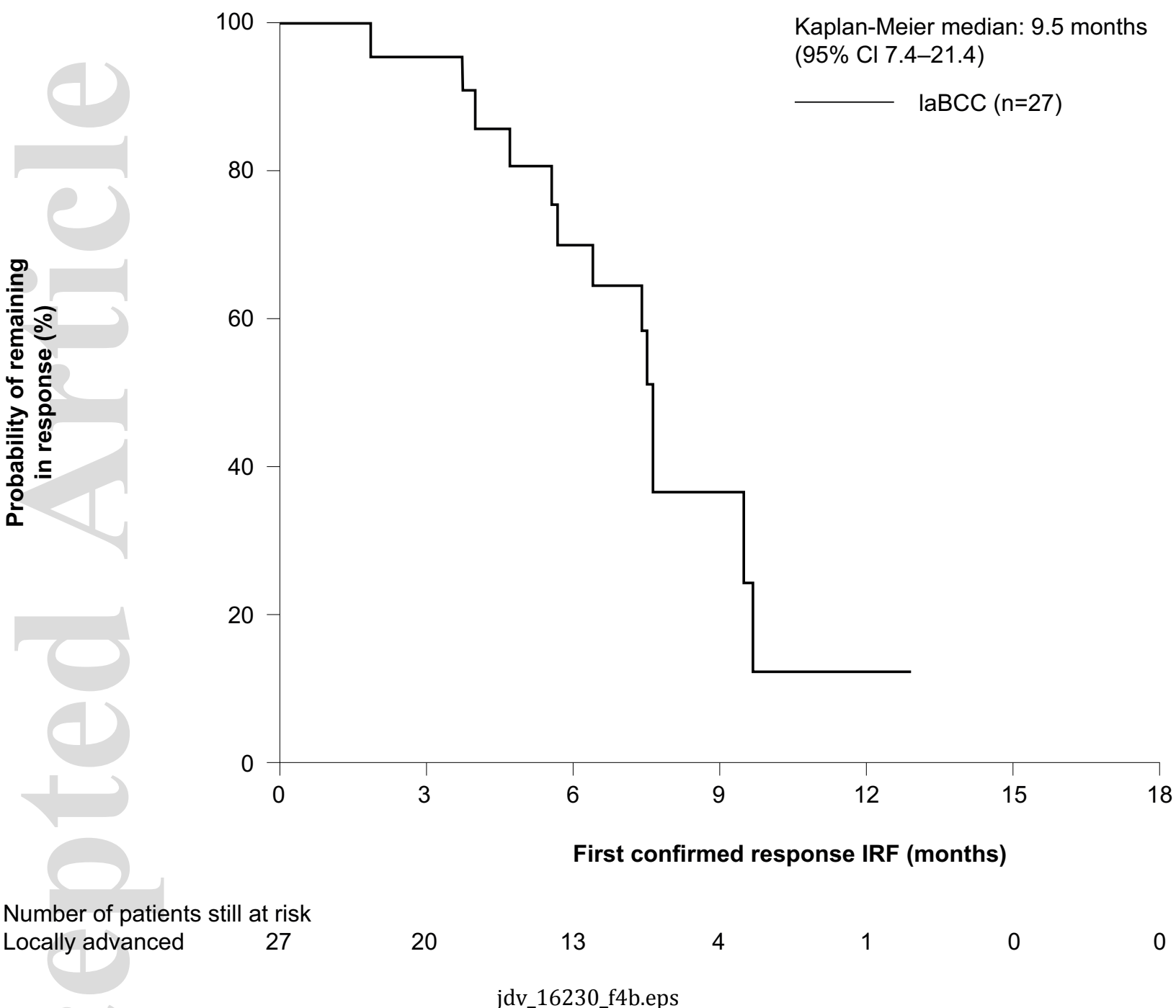
Number of patients still at risk

Time since response (months)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
laBCC	37	35	31	23	21	18	11	9	7	7	7	7	6	5	1	1	1	1	0

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a)

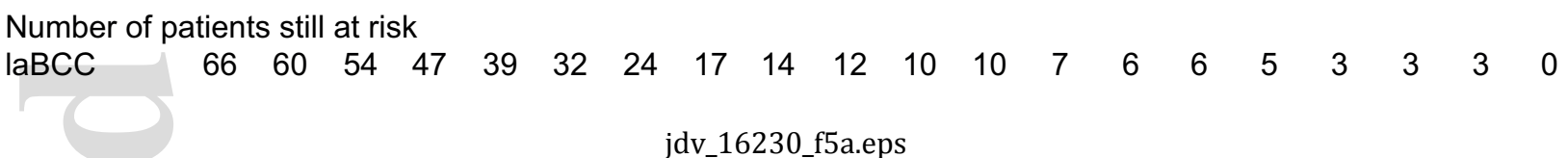
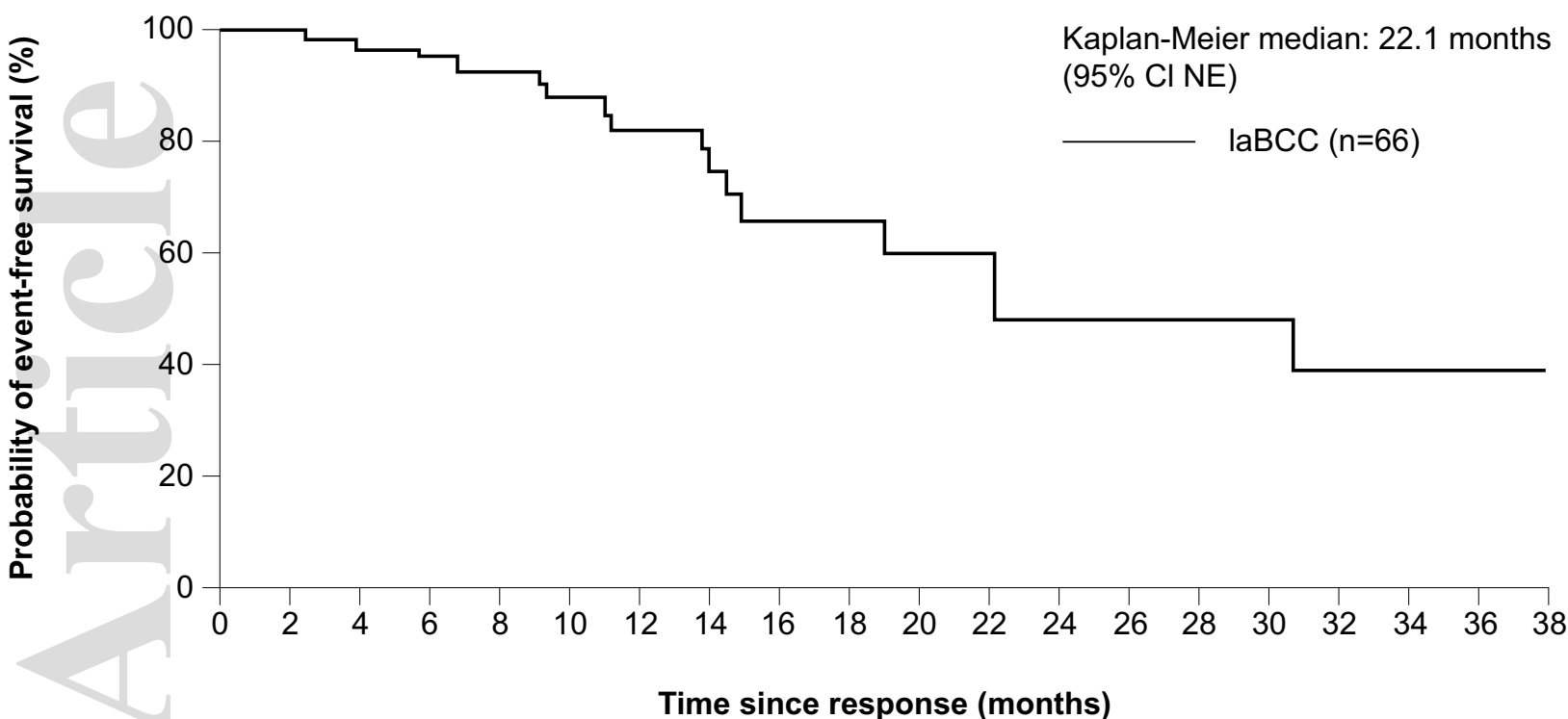
Figure 4. Duration of response (DOR) in patients with locally advanced basal cell carcinoma lesion (laBCC) in the BOLT and ERIVANCE studies. a) Kaplan-Meier plot of DOR in patients with laBCC treated with sonidegib 200 mg QD (n=37) by central review in the BOLT study;\* B) Kaplan-Meier plot of DOR in patients with laBCC treated with vismodegib 150 mg QD (n=27) by central review in the ERIVANCE study.†CI, confidence interval; NE, not estimable. \*Adapted from "Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study" by JT Lear, et al. [CC BY-NC 4.0].†Adapted from European Medicines Agency. EMA/297688/2013 – Erivedge: EPAR - Public assessment report, April 2013.



b)

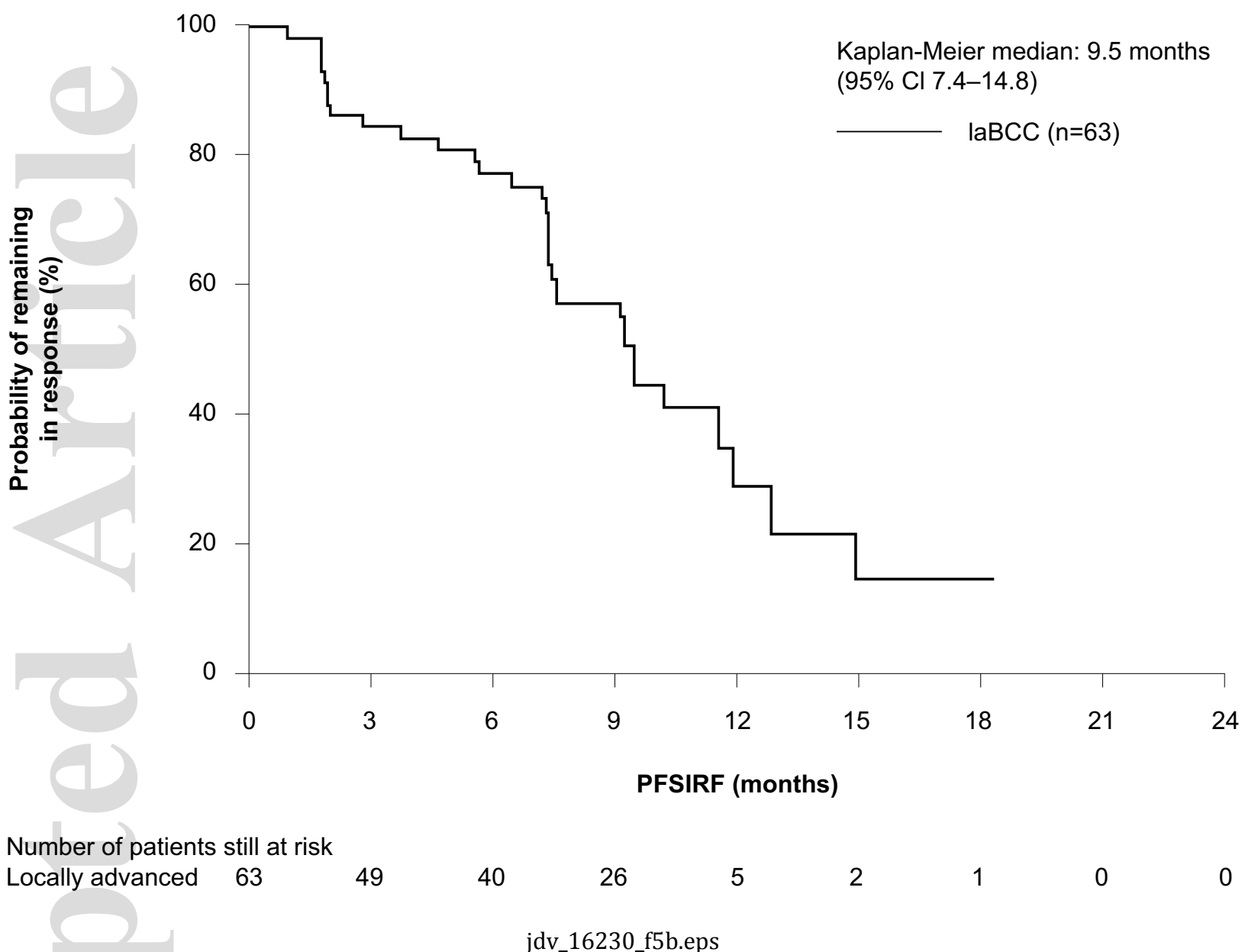
Figure 4. Duration of response (DOR) in patients with locally advanced basal cell carcinoma lesion (laBCC) in the BOLT and ERIVANCE studies. a) Kaplan-Meier plot of DOR in patients with laBCC treated with sonidegib 200 mg QD (n=37) by central review in the BOLT study;\* B) Kaplan-Meier plot of DOR in patients with laBCC treated with vismodegib 150 mg QD (n=27) by central review in the ERIVANCE study.†CI, confidence interval; NE, not estimable. \*Adapted from "Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study" by JT Lear, et al. [CC BY-NC 4.0].†Adapted from European Medicines Agency. EMA/297688/2013 – Erivedge: EPAR - Public assessment report, April 2013.





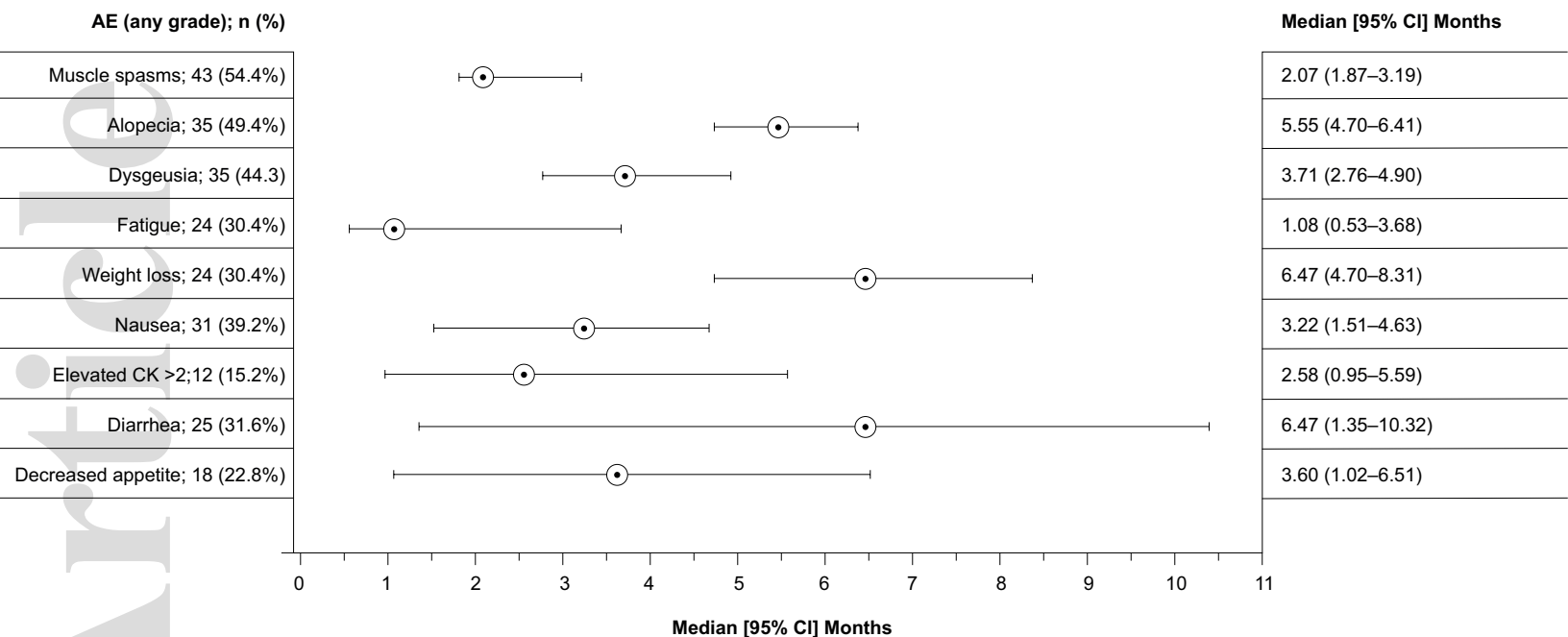
a)

Figure 5. Progression-free survival (PFS) in patients with locally advanced basal cell carcinoma lesion (laBCC) in the BOLT and ERIVANCE studies by central review: a) Kaplan-Meier plot of PFS in patients with laBCC treated with sonidegib 200 mg QD (n=66) by central review in the BOLT study;\* b) Kaplan-Meier plot of PFS in patients with laBCC treated with vismodegib 150 mg QD (n=63) by central review in the ERIVANCE study.† CI, confidence interval; NE, not estimable; QD, once daily.\*Adapted from "Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study" by JT Lear, et al. [CC BY-NC 4.0].†Adapted from European Medicines Agency. EMA/297688/2013 – Erivedge: EPAR - Public assessment report, April 2013.



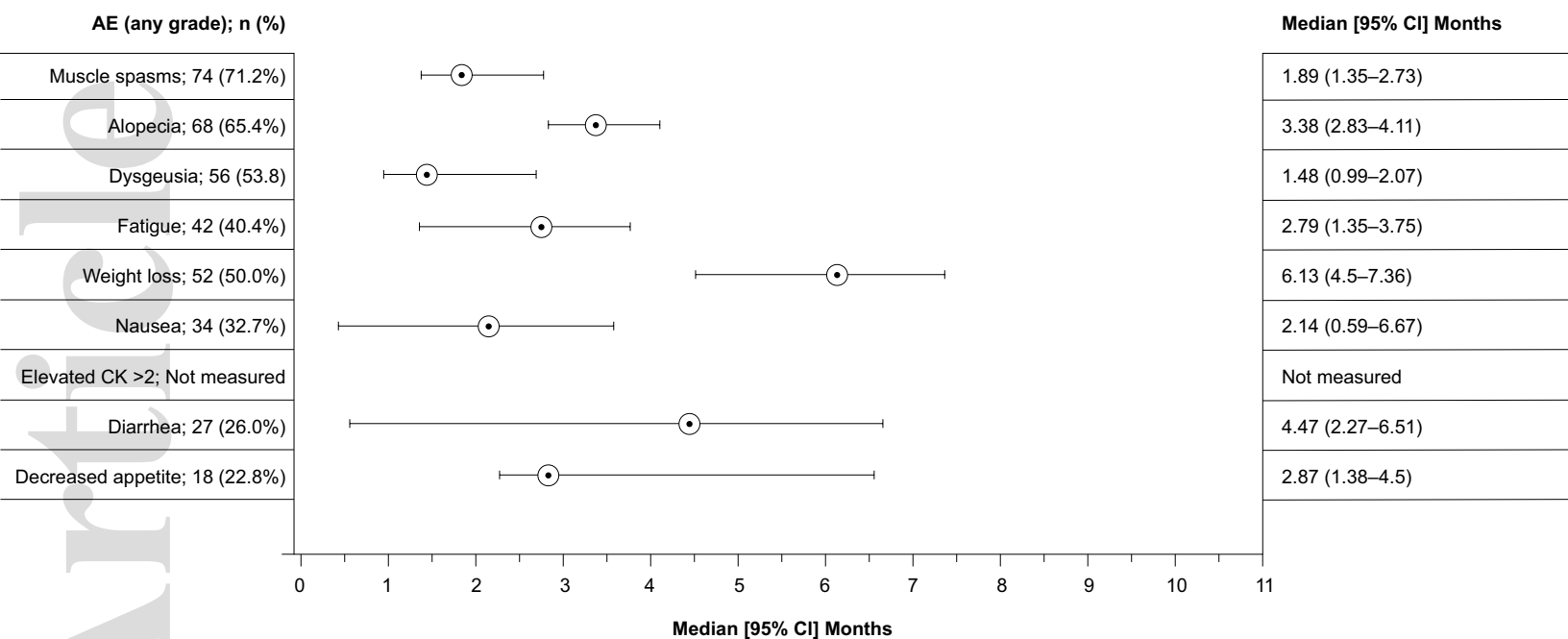
b)

Figure 5. Progression-free survival (PFS) in patients with locally advanced basal cell carcinoma lesion (laBCC) in the BOLT and ERIVANCE studies by central review: a) Kaplan-Meier plot of PFS in patients with laBCC treated with sonidegib 200 mg QD (n=66) by central review in the BOLT study;\* b) Kaplan-Meier plot of PFS in patients with laBCC treated with vismodegib 150 mg QD (n=63) by central review in the ERIVANCE study.† CI, confidence interval; NE, not estimable; QD, once daily.\*Adapted from "Long-term efficacy and safety of sonidegib in patients with locally advanced and metastatic basal cell carcinoma: 30-month analysis of the randomized phase 2 BOLT study" by JT Lear, et al. [CC BY-NC 4.0].†Adapted from European Medicines Agency. EMA/297688/2013 – Erivedge: EPAR - Public assessment report, April 2013.



a)

Figure 6. Time to onset and frequency of common adverse events (AEs) at 21 months in patients with locally advanced basal cell carcinoma lesion (laBCC) and metastatic basal cell carcinoma lesion (mBCC) in the BOLT and ERIVANCE studies. a) Graph of time to onset and frequency of common AEs in patients with laBCC and mBCC treated with sonidegib 200 mg QD (n=79).15,30 b) Graph of time to onset and frequency of common AEs in patients with laBCC and mBCC treated with vismodegib 150 mg QD (n=104).26,29AE, adverse events; CI, confidence interval; QD, once daily.



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b)

Figure 6. Time to onset and frequency of common adverse events (AEs) at 21 months in patients with locally advanced basal cell carcinoma lesion (laBCC) and metastatic basal cell carcinoma lesion (mBCC) in the BOLT and ERIVANCE studies. a) Graph of time to onset and frequency of common AEs in patients with laBCC and mBCC treated with sonidegib 200 mg QD (n=79).15,30 b) Graph of time to onset and frequency of common AEs in patients with laBCC and mBCC treated with vismodegib 150 mg QD (n=104).26,29AE, adverse events; CI, confidence interval; QD, once daily.